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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,874	11/13/2003	Tian-Li Wang	001107.00391	8148

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	**PAPER NUMBER**
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,874	WANG ET AL.	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-24 and 37-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *87,89 and 90* is/are allowed.

6)☒ Claim(s) *1,3-5,10-13,15,18,20,24,37-38,40-42,47-50,52,56,58-86,88 and 91* is/are rejected.

7)☒ Claim(s) *6-9,14,16,17,19,21-23,39,43-46,51,53-55 and 57* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1, 37, 75 and 86-89 have been amended, and claims 2 and 25-36 have been cancelled in the amendment filed 11/15/2006. Claims 1, 3-24, 37-91 are under examination.

Specification

The specification has been amended to correct use of browser-executable code, the objection to the specification is withdrawn.

Claim Rejections - 35 USC § 102

The rejection of claims 25-34 and 36 are rejected under 35 U.S.C. 102(b) has been mooted by the cancellation of claims 25-34 and 36.

Claim Rejections - 35 USC § 112

Claims 1, 37 and 86-89 have been amended and claims 30-33 have been cancelled. The rejection of claims 1-24, 30-34, 37-58 and 86-89 under 35 U.S.C. 112, second paragraph has been withdrawn. The rejection of cancelled claims 30-34 has been mooted.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-85 and 91 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 11/15/2006 and for reasons outlined below.

Applicants submit that the specification discloses comparing the number of tags within a window to identify a difference in the number of tags within the window and cites the instant specification at paragraph 6. Applicants submit that because the method of the invention is useful as a genome-wide analysis (see [17]) typically many such comparisons would be performed. Applicants submit that the claims are open to comparing in one or more windows. Applicants submit that the originally filed specification provides additional support for the recitations in current claim 59-85 and 91 at originally filed claims 1 and 37 which recite, "comparing the number of a plurality of sequence tags...wherein the plurality of sequence tags are within a window of sequence tags..." (emphasis added). Applicants submit that the originally filed application discloses comparisons within a single window.

Applicant's arguments filed 11/15/2006 have been fully considered but they are not persuasive. Claims 59, 75 and 91 are independent claims. Claims 59 and 75 comprise the steps of "enumerating the pieces within a plurality of windows" and then "comparing a first number of pieces enumerated within one of said windows".

Claim 75 comprises the step of "enumerating the pieces with a plurality of windows of fixed size" and " comparing a first number of prices enumerated within a window". As discussed in the previous Office Action, the claims are drawn to enumerating pieces in many windows and then only comparing the number of pieces in one of the windows. The specification does not provide support for a method with these limitations.

The specification at paragraph 6 as cited by Applicant does disclose comparing the number of tags within a single window and does provide support for enumerating tags in one window as one embodiment of the invention, however it does not provide support for a method of one window of a plurality of windows that have been enumerated and comparing the data from only one window to one window of a reference cell when many windows have been enumerated. The general disclosure of utility of the inventive method (see paragraph [0017]) as a genome-wide analysis, which may infer that many such comparisons would be performed, does not sufficiently provide support for the specific methods as claimed.

Although Applicants submit that the claims are open to comparing in one or more windows and that the originally filed application discloses comparisons within a single window, the disclosure does not provide support for comparing within a single window in the context of a method wherein a plurality of windows have been enumerated but then not all are compared. Applicants submit that the originally filed specification provides additional support for the recitations in current claim 59-85 and 91 at originally filed claims 1 and 37, the methods of original claims 1 and 37 do not include the limitation

that a plurality of windows have been enumerated, only a plurality of sequence tags within a window.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 10-13, 15, 18, 20, 24, 37-38, 40-42, 47-50, 52, 56, 58, 86 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,498,013 (Velculescu et al, of record), filed 7/27/2001, in view of Dunn et al (Nov. 4, 2002, of record). Rejections of claims 29, 61, 71, 75-76, 81 and 85 under 35 U.S.C. 103(a) are withdrawn. Claims 47-50 are dependent on the method of claim 37 and have been newly added to this rejection. Claims 1, 86 and 88 have been amended to overcome indefinite language and therefore claims 1, 3-4, 10-13, 18, 20, 24, 86 and 88 are now newly added to this rejection. Claims 5, 15 and 40-41 were previously withdrawn from this rejection and are now reinstated.

This rejection is being maintained for reasons of record in the previous Office Action, mailed 11/15/2006 and for reasons outlined below.

Applicants submit that Velculescu is cited for teaching long SAGE technique in which RNA expression is analyzed by making sequence tags, dimerizing them, concatenating them, and enumerating them. Applicants submit that Velculescu is cited

as teaching enumeration of less than 100% of the sequence tags in Example 1 (col. 15, lines 30-67). Dunn is cited as teaching generation of sequence tags from genomic DNA. The rejection posits that it would have been obvious for one or ordinary skill in the art to modify the method of Velculescu to use genomic DNA, as taught by Dunn. Applicants submit that the rejection must fail because it fails to teach all elements of the claim. It is fundamental that a *prima facie* case of obviousness must provide prior art teachings that cumulatively demonstrate all elements of the claimed invention. Applicants cite M.P.E.P. §2143. Applicants submit that the applied combination of references fails to teach the step of comparing a first number of copies of a plurality of sequence tags to a second number of copies of said plurality of sequence tags, where *the plurality of sequence tags are within a window of sequence tags which are calculated to be contiguous in the genome*.

Applicants submit that the most recent Office Action (mailed May 17, 2006) does not specifically address this limitation, but the prior Office Action (mailed November 16 2005) does. Applicants submit that the 11/16/2005 Office Action asserts that Dunn's concatamerized, dimerized tags comprising 10-50 tags "read on a window of sequence tags comprising 10 to 500, and 50 to 1000 contiguous tags" (Office Action of November 16, 2005, at page 9, lines 1-5). However, Applicants submit that the tags in a clone of concatamerized, dimerized tags are not tags which are calculated to be contiguous in the genome. The dimers and the concatamers are *randomly* joined, and thus their order or their presence in a clone provides no information about their contiguity in the genome.

The Office Action of November 16, 2005 further asserts that Dunn teaches, "enumerating the pieces of a plurality of windows for the test cell to pieces for a reference cell" (O. A., Page 10, lines 12-19, citing Dunn at page 1763, col. 1, third paragraph). However, Applicants submit that Dunn does not explicitly or implicitly teach the use of windows. Dunn teaches:

> In summary, the basic GST procedure described here provides a means for genome-wide fingerprinting of chromosomal and episomal DNAs and, by extension, for profiling DNA genomes in natural populations. Like SAGE, it can be performed with equipment available in most molecular biology laboratories. The GST technique can be used, with minor modifications, for long SAGE analysis of eukaryotic mRNAs and might, like AFLP of cDNA (Qin et al. 2001; Donson et al. 2002.), be adaptable for profiling gene expression in prokaryotes.

Applicants submit that neither Dunn nor Velculescu teach the use of a window, i.e., a plurality of pieces of genomic DNA which are calculated to be contiguous in the genome of the reference eukaryotic cell. Applicants submit that since no cited reference provides this teaching, the *prima facie* case must fail.

Applicant's arguments filed 11/15/2006 have been fully considered but they are not persuasive. The instant specification defines windows as "groups of sequence tags which are genomically clustered". Further, the instant specification discloses that the term "adjacent or contiguous as used herein to describe tags does not imply that the nucleotides of one tag are contiguous with the nucleotides of another tag, but rather that the tags are clustered in the same areas of the genome" and "virtual tags are associated with locations in the genome" (see paragraph 0022). It is noted that the specification does not disclose limits on how closely a tag must be to another tag in order to be "clustered in the same areas of the genome".

Velculescu et al disclose the SAGE process which is based on the principle that tags contain sufficient information to uniquely identify a transcript from database of cDNA provided it is isolated form a define position within the transcript. Dunn et al teach a method for the analysis of genomic signature tags (GST) for an organism (*Y. pestis*) with a 4.7 Mb genome that has been initially digested with two type II restriction enzymes. Dunn et al also teach that the number of NotI, BamHI and NlaIII cleavage sites were determined *in silico* and then determined that the BamHI enzyme should be used to fragment the *Y. pestis* genome because it was predicted to generate sufficient tags for meaningful data analysis. Dunn et al teach subsequent steps using NlaIII and MmeI to form amplified GST that have been randomly ligated on themselves to form concatamers prior to cloning. Dunn et al teach that tags are easy to identify since they should contain a BamHI recognition site near the 3' end. Dunn et al disclose that the fragments have been numbered according to their order along the DNA (see page 1759, left column, for example). Dunn et al disclose that the GSTs were obtained from predetermined positions in the genomic DNA. Dunn et al know that the GST must be associated with a BamHI recognition site from the *Y. pestis* genome and can be numbered in order. Therefore, the GST concatamers are clustered around the areas of the genome known to have BamHI recognition sites and, since according to the instant disclosure paragraph 0022, the tags do not have to be contiguous with the nucleotides of another tag, the GST can be randomly joined and still meet the limitation of tags are clustered in the same areas of the genome or window. Dunn et al teach that the concatamers were cloned into vectors. While Dunn et al do not use the word "window",

each concatamer in a vector reads on a window comprising a plurality of sequence tags which are calculated to be contiguous (i.e., associated around a BamHI site) in the genome. Therefore Dunn et al does provide this teaching and the rejection is maintained.

The method of claim 1 differs from the method of claim 37 because it comprises the step of comparing the number of copies of a plurality of sequence tags to a second number of copies of a plurality of sequence tags determined for a genome of a reference eukaryotic cell. Claim 37 comprises the step of comparing the number of copies of a plurality of sequence tags to a second number of copies of a plurality of sequence tags calculated to be present in the genome of a reference eukaryotic call.

Velculescu et al disclose an embodiment in which gene expression is compared between pathologic tissue and its normal counterpart (column 22, lines 31-36, in particular), which reads on an embodiment of the claimed method wherein the number of copies of a plurality of sequence tags in a pathologic tissue (i.e. test eukaryotic cells) is compared to a second number of copies of a plurality of sequence tags determined for a genome of a normal counterpart (i.e. reference eukaryotic cells). Therefore the teachings of Velculescu et al in view of Dunn et al (as described above) render the method of **claim 1** obvious.

Velculescu et al teach that some concatamers containing clones used have at least 10 sequence tags of a range of 10-50 tags (see column 15, lines 17-26, for example), which meets the limitation of the claimed method wherein plurality of sequence tags comprising 10-500 contiguous tags and 50 to 1000 contiguous sequence

tags **(claims 3-4 and 40-41)**. Velculescu et al also disclose the use of DLD1 colon cancer cells (column 7, lines 32-37, for example) which is a human colon cancer cell line and meets the limitation of a method wherein the test eukaryotic cell is a human cell and a cancer cell (**claims 5 and 15**).

As discussed above, Dunn et al teach a method of generating tags using NotI, BamHI and NlaIII restriction enzymes, and Velculescu et al teach the use of NlaIII to cleave nucleic acid sequences (see column 15, lines 1-5, for example), which meets the limitation of a method wherein portion are defined by a first restriction endonuclease cleavage site at the first end and a second restriction endonuclease cleavage site at the second end and wherein the second enzyme is NlaIII (**claims 18 and 20**).

Dunn et al teach an embodiment in which the generated sequence tags are ligated together to form concatamers which are cloned into plasmids to generate a library for sequencing analysis, which were enumerated for a total of 5432 sequence tags from the sequenced concatamers (see page 1759, left column, 2nd and 3rd paragraph, for example), which reads on a method comprising a step of determining the sequence of said sequence tags and recording the number of occurrences of individual sequence tags and meets the limitation of **claim 24**.

As discussed in the Office action of 5/11/2006, Velculescu et al teach that computer analysis of human pancreas transcripts set to include only sequences noted as "RNA", produced results for 13,241 sequences. Velculescu et al analyzed this 13,241 subset of sequences using NlaIII as the restriction enzyme. Velculescu et al suggested that 5381 of the 9 bp tags were unique to a transcript or highly conserved

transcript family. Further, Velculescu et al exemplify the method of serial analysis of gene expression (longSAGE) method and only analyze the first 1000 tags (see column 15, lines 30-67, for example). Analysis of 1000 tags out of ~5381 tags is enumeration of ~18% of the sequence tags calculated to be present. Therefore, Velculescu et al teach the claimed methods wherein less than 100%, or less than 50%, or less than 33% or less than 25% or less than 20% of the tags calculated to be present in the genome are enumerated and meet the limitation of claims **10-13 and 47-50.**

Claim 86 is drawn to a method of karyotyping a genome of a test eukaryotic cell, comprising the step of comparing a first number of copies of a plurality of sequence tags to a second number of copies of said plurality of sequence tags determined to be present in the genome of the test cell wherein the plurality of sequence tags comprises 50 to 1000 contiguous sequence tags, wherein a difference between the first number and the second number indicates a karyotypic difference between the test eukaryotic cell and the reference eukaryotic cell. Claim 86 comprises the limitations of the method of claim 1 and the additional limitation of claim 4. As described in the previous Office actions and above, the teachings of Velculescu et al in view of Dunn et al (as described above) render the method of **claim 86** obvious.

Claim 88 is drawn to a method of karyotyping a genome of a test eukaryotic cell, comprising the step of comparing a first number of copies of a plurality of sequence tags to a second number of copies of said plurality of sequence tags calculated to be present in the genome of the test cell, wherein the plurality of sequence tags comprises 50 to 1000 contiguous sequence tags, wherein a difference between the first number and the

second number indicates a karyotypic difference between the test eukaryotic cell and the reference eukaryotic cell. Claim 88 comprises the limitations of the method of claim 37 and the additional limitation of claim 41. As described in the previous Office actions and above, the teachings of Velculescu et al in view of Dunn et al (as described above) render the method of **claim 88** obvious.

It should be noted that the disclosure does not specifically define karyotypic abnormality in the specification and therefore karyotypic abnormality will be interpreted as to mean a difference in the number of sequence tags by insertion or deletion between a test eukaryotic cell and the human genome.

Conclusion

Claims 87, 89- 90 are allowed. Claims 6-9, 14, 16-17, 19, 21-23, 39, 43-46, 51, 53-55 and 57 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
Examiner
2/15/2007

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PRIMARY EXAMINER